REMARKS

Claims 1-18 were originally filed in the present case. In the Office Action dated July 2, 1999, the Examiner made a number of arguments and rejections. For clarity, the rejections at issue are set forth by number in the order they are herein addressed:

(1) Claims 1-6 stand rejected under 35 U.S.C. §101 as allegedly drawn to non-statutory subject matter.

(2) Claim 1 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

(3) Claims 1-3 and 7-15 were rejected under 35 U.S.C. §103(a) as allegedly obvious.

(4) Claims 3-6 and 16-18 stand rejected under 35 U.S.C. §103(a) as allegedly obvious.

Applicant believes the present amendments and following remarks traverse the Examiner's rejections. These remarks are presented in the same order as the above rejections.

I. THE CLAIMS COVER STATUTORY SUBJECT MATTER

The Examiner rejected Claims 1-6 under 35 U.S.C. §101 as allegedly drawn to non-statutory subject matter by encompassing "antibodies as they occur in nature" without a showing of the "hand of man" in their isolation. (Office Action, pg. 2). Applicant must respectfully disagree. The present invention relates to ***particular*** combinations of antibodies and their therapeutic use in mammals. The specification clearly describes a method for producing, isolating, and purifying said antibodies, as well as a therapeutic methods of their use. Clearly, the antibodies and methods in the present invention are sufficiently acted upon by the "hand of man" to distinguish them from those "occur[ing] in nature." As such, the requirements of 35 U.S.C. §101 are satisfied. Thus, the Examiner's rejection of Claims 1-6 is unwarranted.

Nonetheless, in order to further business interests and the prosecution of the present Application, without acquiescing to the Examiner's arguments, and while reserving the right to prosecute the original claims in the future, Applicant amends Claim 1, to recite that the antibodies are purified. Support for this amendment is found at pg. 8, lines 3-20, in the instant specification. Thus, the rejection to Claims 1-6 should be withdrawn.

II. THE CLAIMS ARE DEFINITE

The Examiner rejected Claim 1 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to "particularly point out and distinctly claim the subject matter which Applicant regards as his invention." (Office Action, pg. 2). This standard is "essentially a requirement for precision and definiteness of claim language rather than a limitation on the scope of the claim, which may be vast without being imprecise or indefinite."[1] Moreover, as noted by the Court in *In re Swinehart*, 439 F.2d 210 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought. (MPEP § 2173.01).

The Examiner rejected Claim 1 as indefinite for reciting "a composition comprising a *mixture* of antibodies." (Office Action, pg. 2). The Applicant must respectfully disagree.

Nonetheless, in order to further business interests and the prosecution of the present Application, without acquiescing to the Examiner's arguments, and while reserving the right to prosecute the original claims in the future, Applicant amends Claim 1, as suggested by the Examiner, to obviate this rejection. Specifically, Applicant acknowledges the Examiner's suggestion to amend Claim 1 by deleting the allegedly indefinite "mixture" limitation. Consequentially, the Examiner should withdraw this rejection.

III. NO *PRIMA FACIE* CASE OF OBVIOUSNESS IS ESTABLISHED FOR CLAIMS 1-3 AND 7-15

The Examiner rejected Claims 1-3 and 7-15 as allegedly obvious under Starnes *et al.*, (Starnes *et al.*, J. of Immun. Vol. 145, No. 12 [1990]), and Doherty *et al.*, (Doherty *et al.*, J. of Immun. Vol. 149, No. 5 [1992]). Applicant respectfully disagrees.

The combination of references cited by the Examiner fails to establish a *prima facie* showing of obviousness as required by MPEP § 2143. A *prima facie* case of obviousness requires the Examiner to cite a reference(s) which (a) discloses all the elements of the claimed invention, (b) suggests or motivates one skilled in the art to combine or modify those elements to yield the claimed combination, and (c) provides a reasonable expectation of

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[1] *In re Hyatt*, 708 F.2d 712, 714, 218 USPQ 195, 197 (Fed. Cir. 1983), *quoting In re Borkowski*, 422 F.2d 904, 909, 164 USPQ 642, 645 (C.C.P.A. 1970).

success should the claimed combination be carried out.[2] Failure to establish ***any one*** of these requirements precludes a finding of *prima facie* obviousness, and without more, entitles Applicant to allowance of the claims at issue. The references cited by the Examiner do not teach all of the elements of the Claims, do not contain a suggestion or motivation to modify or combine teachings, and finally, do not provide a reasonable expectation of success should the combination of references be carried out. Thus, the Applicant must respectfully traverse the Examiner's rejection.

A. The Examiner Improperly Combined the Starnes and Doherty References Without Motivation or Suggestion

As previously mentioned, to establish *prima facie* obviousness, the Examiner must point to some motivation or suggestion within the references themselves, or within the knowledge generally available to one of ordinary skill in the art at the time of invention, to combine or modify the references.[3] Merely because the references could be combined or modified does not render the resultant combination obvious unless the prior art suggested the combination.[4] Applicant submits the Examiner has not provided a basis for combining these references.

The Examiner cited Starnes *et al.*, as teaching two murine sepsis challenge models; in the these models, either rat anti-mouse IL-6 antibodies, ***or*** rabbit anti-mouse TNF-α antibodies, when administered prior to *E.coli* LPS challenge, decreased morbidity. (Office Action, pg. 3). However, the Examiner subsequently admitted: "Starnes et al., do not disclose a composition comprising both antibodies to TNF-α and IL-6 or a method of treatment with such composition." (Office Action, page 3). The Examiner next cited Doherty *et al.*, for teaching anti INF-γ antibodies and anti TNF-α antibody administration to LPS challenged mice. (Office Action, pg. 3-4). Here, as above, the Examiner admitted that Doherty *et al.*, did not disclose a composition comprising anti-INF-γ and anti-TNF-α antibodies because

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[2] *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

[3] *See* MPEP §2143.0; *See also In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

[4] *See* MPEP §2143.01; *See also In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990).

mice were "treated with ***either*** anti-INF-γ polyclonal antibodies, or anti-TNF-α polyclonal antibodies." (Office Action, pg. 3-4). (emphasis added) Hence, the Examiner admitted the ***combined*** references failed to teach or suggest the present invention as claimed, "***Neither*** Starnes *et al.*, nor Doherty *et al.*, disclose a composition comprising polyclonal antibodies directed against TNF-α, IL-6 and IFN-γ and ***a method of treatment*** with such composition." (Office Action, pg 4). (emphasis added)

Despite these telling admissions, the Examiner, in an attempt to establish a motivation or suggestion to combine Starnes *et al.*, and Doherty *et al.*, stated:

> One of ordinary skill in the art would have been motivated at the time of the invention to develop a composition comprising antibodies against TNF-α, IL-6, and IFN-γ and a method of treating sepsis with said composition, because Starnes et al and Doherty et al demonstrated that these antibodies when used ***separately*** showed beneficial effects against septic shock, thus, combining them in one therapeutic composition ***would be expected to give synergistic and more robust effect*** against septic shock, it would also be easier to administer one composition to a patient than it is to administer three different compositions. (Office Action, pg. 4-5). (emphasis added)

Applicant submits that the Examiner has failed to establish a motivation to combine for several reasons.

First, neither reference cited by the Examiner suggests a therapeutic composition comprising the antibodies as ***combined*** in the present invention. The law is clear, the mere fact that two independent references teach in the same field of endeavor, without a clear suggestion in either reference to combine teachings, is not a legally sufficient basis for *prima facie* obviousness.[5]

Second, the Examiner has failed to cite any references supporting the conclusion that administering these antibodies in combination "would be expected to give synergistic and more robust effect against septic shock." (Office Action, pg. 5). In fact, neither Starnes *et al.*, nor Doherty *et al.*, even discuss the possibility of co-administering the antibodies. The Examiner cannot maintain this rejection without citing to some reference in the prior art.[6]

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[5] *Ex parte Dussard*, 7 USPQ2d 1818, 1820 (PTO Bd. Pat. App. & Int'f., 1988) ("The mere fact that the prior art could be modified in the manner proposed by the Examiner would not have made the modification obvious unless the prior art suggested the desirability of the modification.").

[6] *See* MPEP § 2144.03.

B. The Combined References do not Teach Every Claim Limitation

Under MPEP § 2143.03, to establish a *prima facie* case of obviousness the combined art must teach all claim limitations. Applicant submits that the combination of Starnes *et al.*, and Doherty *et al.*, does not teach all the limitations found in Claims 1-3 and 7-15. In particular, Applicant submits that neither reference teaches the combination of two anti-cytokine antibodies (let alone the combination of anti-TNF and anti-IL-6 antibodies).

The Examiner admits the Starnes et al. reference does "not disclose a composition comprising both antibodies to TNF-α and IL-6 or a method of treatment with such composition." (Office Action, pg. 3). Furthermore, the examiner cites Doherty *et al.* as teaching treatments "with ***either*** anti-IFN-γ polyclonal antibodies ***or*** anti-TNF-α polyclonal antibodies." (Office Action, pg. 3-4). (emphasis added) Thus, the Examiner admits that the references when combined do not "disclose a composition comprising polyclonal antibodies directed against TNF-α, IL-6, and IFN-γ." (Office Action, pg. 4). By the Examiner's own admissions, neither reference teaches a composition wherein more than one type of anti-cytokine antibody are co-administered. As such, the Examiner has failed to teach all the limitations of Claims 1-3 and 7-15. Consequently, a *prima facie* case of obviousness has not been established and this rejection should be withdrawn.

C. Even if References are Combined They do not Provide a Reasonable Expectation of Success

In order to establish a *prima facie* case of obviousness the prior art must, when combined, lead to a reasonable expectation of successfully producing the invention. (MPEP § 2143.02). Applicant respectfully submits that one of ordinary skill in the art would not reasonably expect to produce the claimed invention by combining the cited references. Applicant directs the Examiner's attention to the failure data in the specification and the above accompanying discussion.

1. The Examiner Disregarded the Applicant's Failure Data

The Examiner ignored the Applicant's failure data. Applicant points to Table 3 in the specification of the present invention, where: 1) anti-IFN-γ antibodies administered alone (60 minutes post challenge) failed to save any test animals; and 2) the combination of anti-TNF

and anti-IFN-γ antibodies (administered 60 minutes post challenge) failed to save any test animals.

Contrary to Applicant's results in Example 1, shown above, the Doherty *et al.*, reference cited by the Examiner showed decreased morbidity in test animals upon administration of anti-IFN-γ antibodies alone. Thus, Doherty et al., actually suggests the singular administration of anti-IFN-γ antibodies and not the co-administration of anti-IFN-γ antibodies with other anti-cytokine antibodies disclosed by the present invention.

Furthermore, contrary to Applicant's results in Example 2, shown above, the Examiner cited both Starnes *et al.*, and Doherty *et al.*, as teaching administration of anti-TNF-α antibodies alone decreases morbidity in test animals; moreover, the Examiner cited Doherty *et al.*, as teaching the administration of anti-IFN-γ antibodies alone also decreases morbidity in test animals. From here, the Examiner implicitly argued that because these references ***individually*** taught decreased morbidity in respective test animals, that when their teachings are combined they must also decrease morbidity in test animals. Again, as shown in Applicant's Example 2, this is not the case. Applicant submits that the failure data in the instant specification underscores the ***non-obviousness of the present invention***. The Examiner's rejection is thus unwarranted.

2. "Obvious to Experiment" is not the Standard for Obviousness

The Federal Circuit has held that "obvious to experiment" is not the standard for obviousness.[7] The Federal Circuit has made it very clear that one must determine whether "the prior art would have suggested to one ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art."[8]

Applicant submits that the Examiner wrongfully reviewed the present invention under an impermissible "obvious to experiment" standard. The prior art does not suggest a reasonable chance of success for compositions combing the relevant anti-cytokine antibodies nor did the prior art suggest a reasonably successful therapeutic method for the use of such

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[7] *See In re Dow Chemical*, 5 USPQ 2d 1529, 1532 (Fed. Cir. 1988).

[8] *Id* at 1531. (emphasis added)

composition. Applicant, again, directs the Examiner's attention to the failure data presented in the specification.

Thus, the Examiner has not established that a reasonable expectation of success existed in the prior art for practicing the present invention, hence, a *prima facie* case of obviousness has not been established. Applicant respectfully requests that this rejection be withdrawn.

IV. NO *PRIMA FACIE* CASE OF OBVIOUSNESS IS ESTABLISHED FOR CLAIMS 3-6 AND 16-18

The Examiner rejected Claims 3-6 and 16-18 as obvious over the combination of Starnes *et al.*, and Doherty *et al.*, in view of Emery *et al.*, (U.S. Pat. No. 5,420,253) ("'253 Patent"). Applicant respectfully traverses this rejection.

The combination of references referred to by the Examiner fails to provide a *prima facie* case of obviousness. In traversing the Examiner's instant rejection of Claims 3-6 and 16-18, the Applicant incorporates the above arguments traversing the Examiner's obviousness rejection of Claims 1-3 and 7-15. Applicant submits, as above, that: 1) the combination of Starnes *et al.*, and Doherty *et al.*, does not teach all of the claim limitations (i.e., a composition with more than one anti-cytokine antibody); 2) that the Examiner has not demonstrated a suggestion for combining the references; 3) the Examiner ignored the Applicant's failure data; and 4) that the references, if combined, would not lead one reasonably skilled in the art to form a reasonable expectation of success.

A. The Examiner improperly combined the Starnes and Doherty references in view of the Emery Patent without motivation or suggestion

The Examiner in rejecting Claims 1-3 and 7-15, relies on the above mentioned combination of the Starnes *et al.*, and Doherty *et al.*, references in light of the '253 Patent to Emery *et al.* Applicant submits that the Examiner had no motivation to combine these references.

The Examiner cites the '253 Patent as teaching a method of "purifying high yields of IgG IgY) immunoglobulin from chicken egg yolk." (Office Action, pg. 5). The Examiner stated that: "Emery *et al.*, *suggest*[*s*] that anti-TNF antibodies could be produced by said method [administering TNF as an immunogen to chickens]...and that these antibodies could be administered." (Office Action, pg. 5). (emphasis added) Next, the Examiner cites a portion

of the '253 Patent as indicating that these *suggested* "antibodies could be administered...to immunize animals and/or humans." (Office Action, pg. 5).

While the '253 Patent discloses a method for purifying IgG immunoglobulins from egg yolks, this alone, does not make up for the reference's lack of teaching a combination of more than one anti-cytokine antibodies (let alone anti-TNF antibodies and IL-6). This fact is tacitly admitted by the Examiner who only cites the reference as discussing anti-TNF antibodies. Where a reference merely teaches that IgG immunoglobulins may be isolated from egg yolks,[9] the teaching is not relevant to the use of a composition comprising anti-TNF-α, anti-INF-γ, and anti IL-6 antibodies for the treatment of sepsis in mammals.

B. The Literature Indicates that Combinations May Be Problematic

While the Examiner has taken the position that it would be obvious to use a combination of antibodies *with success*, the literature does not support such a conclusion. The publication by Opal *et al.* illustrates this point (attached hereto at Tab A). Opal *et al.* were encouraged by reports by others involving combinations of inhibitors (Tab A, page 1415, right hand column). However, when actual experiments were performed, Opal *et al.* concluded that "[c]ombination anticytokine therapy may exacerbate systemic infection and worsen [the] outcome in experimental sepsis." (Tab A, last line of the Abstract).

Applicants submit that the Opal *et al.* report underscores the empirical nature of applicants discovery. The Opal *et al.* report would indicate that no benefit is achieved with a combination and -- indeed -- combination therapy can be problematic. However, using the particular combination claimed, the present applicants have generated data that shows a benefit to the use of a specific combination. Based on the Opal *et al.* report, one would not predict such a result. Only after the data is actually generated for the specific combination can one know whether success can be achieved.

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[9] This is not to say that the applicants believe that the reference has any bearing on immunization with other antigens. That is to say, making chicken antibody to a particular antigen is not assured simply because there has been success with a different antigen. Indeed, the inventors have encountered problems with particular cytokines.

It is submitted that, where success cannot be predicted, an obviousness rejection is not appropriate. Given the limitation of the pending claims to specific combinations, applicants submit that the Examiner's obviousness rejections should be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (617)-252-3353.

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